Abstract

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Abstract: *DESCRIPTION* (provided by applicant): Alzheimer's disease is a dementing illness of the elderly defined by the appearance of characteristic lesions in the brain. It differs from other dementias in the protein composition of the lesions and by their hierarchical emergence in distinct cortical and subcortical regions. For these reasons, their spatial and temporal distributions facilitate differential diagnosis and staging of disease. Neurofibrillary lesions have special utility in this regard. They are composed of tau, a microtubule-associated protein that normally functions to promote tubulin assembly, microtubule stability, and cytoskeletal integrity. Tau that accumulates in neurofibrillary lesions differs from microtubule-associated protein in its state of aggregation. Moreover, fibrillization is accompanied by conformational changes in tau protomers that can be sensed by selective monoclonal antibodies and by small molecules such as thioflavin dyes. These data suggest that tau-bearing lesions present novel binding sites that can be detected with small molecule probes, and potentially exploited to develop ligands capable of selectively detecting their presence. Such agents could have practical usage as contrast agents capable of staging disease pre-mortem, whereas ligands capable of antagonizing aggregation could potentially emerge as therapeutic agents. The present proposal has one Specific Aim to test this hypothesis. Amyloidgenic conformations of tau protein will be subjected to high throughput screening in the Molecular Libraries Screening Centers Network. Active compounds will be subjected to secondary screens capable of quantifying binding affinity and selectivity for tau relative to other aggregating proteins. The ability of selected ligands to inhibit tau aggregation also will be assessed. Successful completion of this project will yield pharmacological agents with the potential to facilitate dissection of the aggregation pathway in biological systems, to clarify the role of filament formation in disease, and to drive early stage diagnosis of Alzheimer's disease.

Thesaurus Terms:
High throughput screening, Alzheimer's disease, Neurofibrillary lesions, tau, tubulin assembly, microtubule stability, cytoskeletal integrity, fibrillization, thioflavin dyes, Amyloidgenic

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